Assessing the robustness of recommendations made in a guideline on specialist neonatal respiratory care in babies born preterm with threshold analysis

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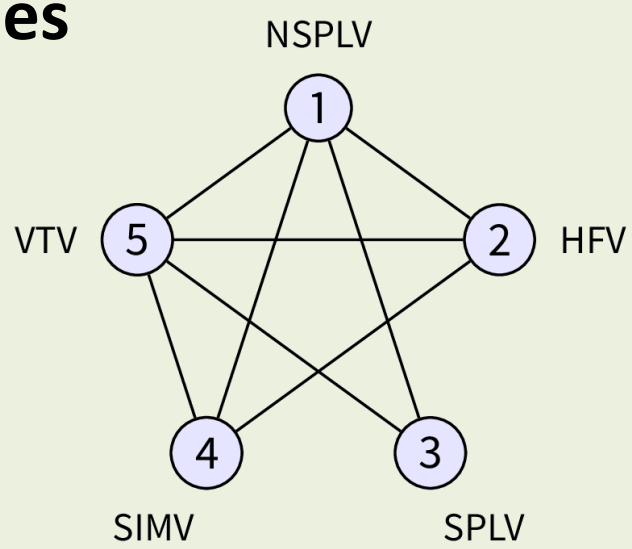
NICE Clinical Guideline: Invasive ventilation for preterm babies

Five interventions

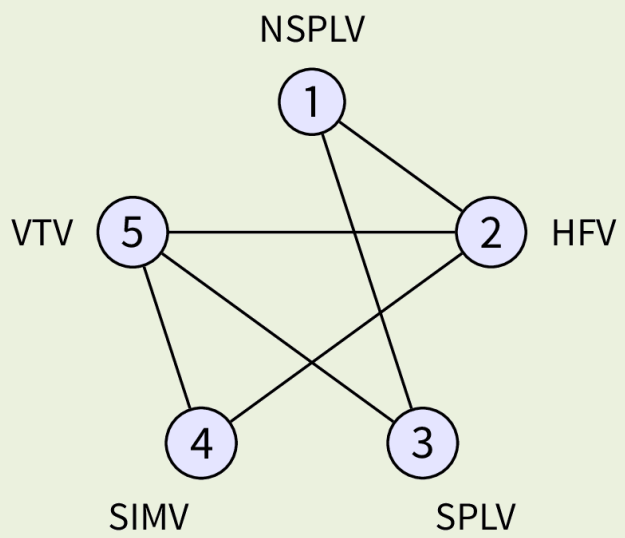
- Non-synchronised pressure limited (NSPLV)
- High frequency (HFV)
- Synchronised intermittent mandatory (SIMV)
- Synchronised pressure limited (SPLV)
- Volume targeted (VTV)

Two outcomes

Mortality



Bronchopulmonary Dysplasia (BPD)



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Network Meta-Analysis (NMA)

- Combines evidence on multiple treatments from several studies
- Arranges treatments on a network structure joined by study evidence
- Provides a coherent set of treatment effect estimates
- Is routinely used to inform clinical guideline recommendations, technology appraisals

Invasive ventilation: Initial recommendations

Invasive ventilation techniques in the neonatal unit

For preterm babies who need invasive ventilation, **use volume-targeted ventilation (VTV)** as the primary mode of respiratory support. If VTV is not effective, **consider high-frequency oscillatory ventilation (HFV)**.

Do not use synchronised pressure-limited ventilation (SPLV) such as…

(NICE guideline NG124)

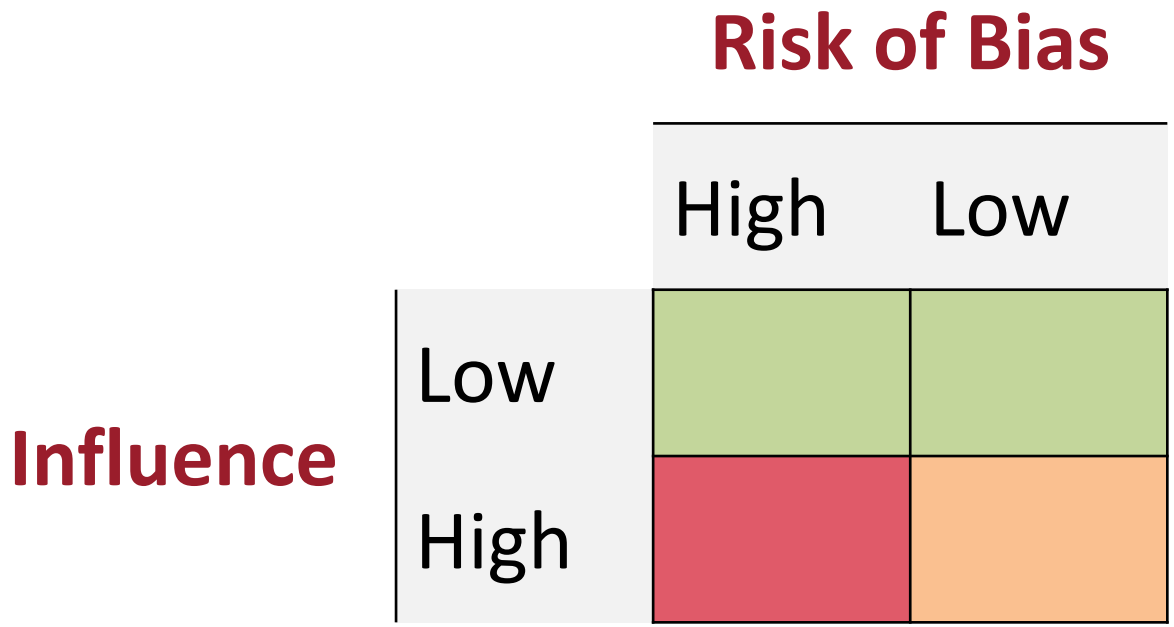
Invasive ventilation: Key concerns for decision makers

- High risk of bias due lack of blinding and treatment switching in all studies
- Concern over strength of “do-not-do” SPLV recommendation based on mortality

Motivation for threshold analysis

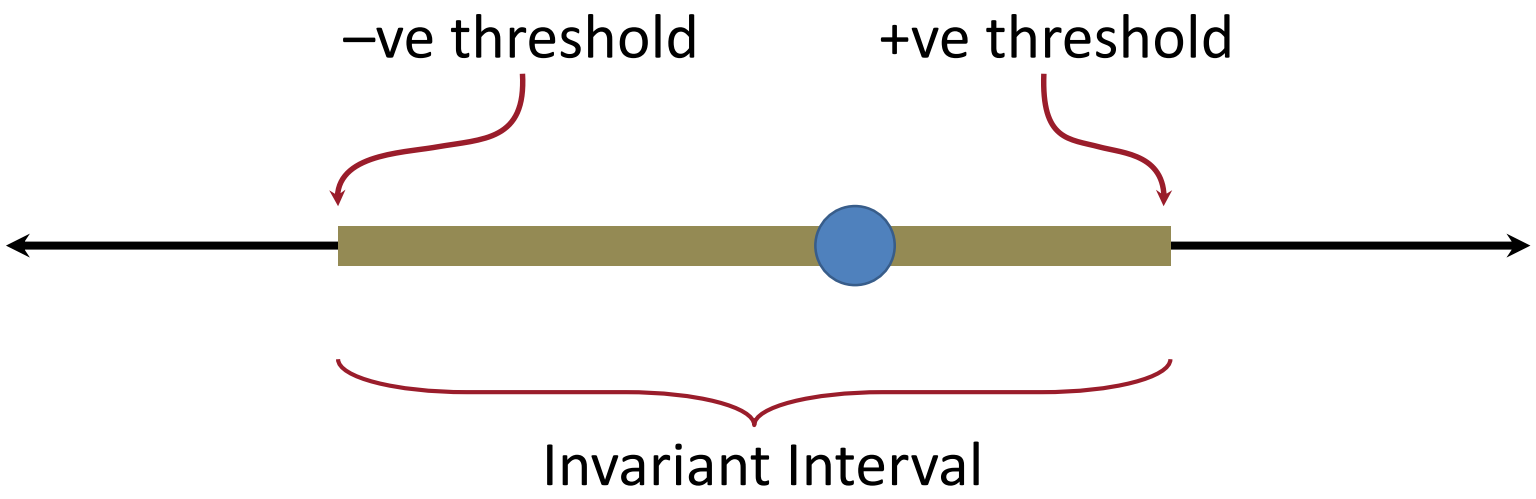
How robust are the recommendations based on NMA?

- Risk of Bias (or evidence quality) is only part of the story…



Threshold Analysis

Create an *invariant interval* for a data point:



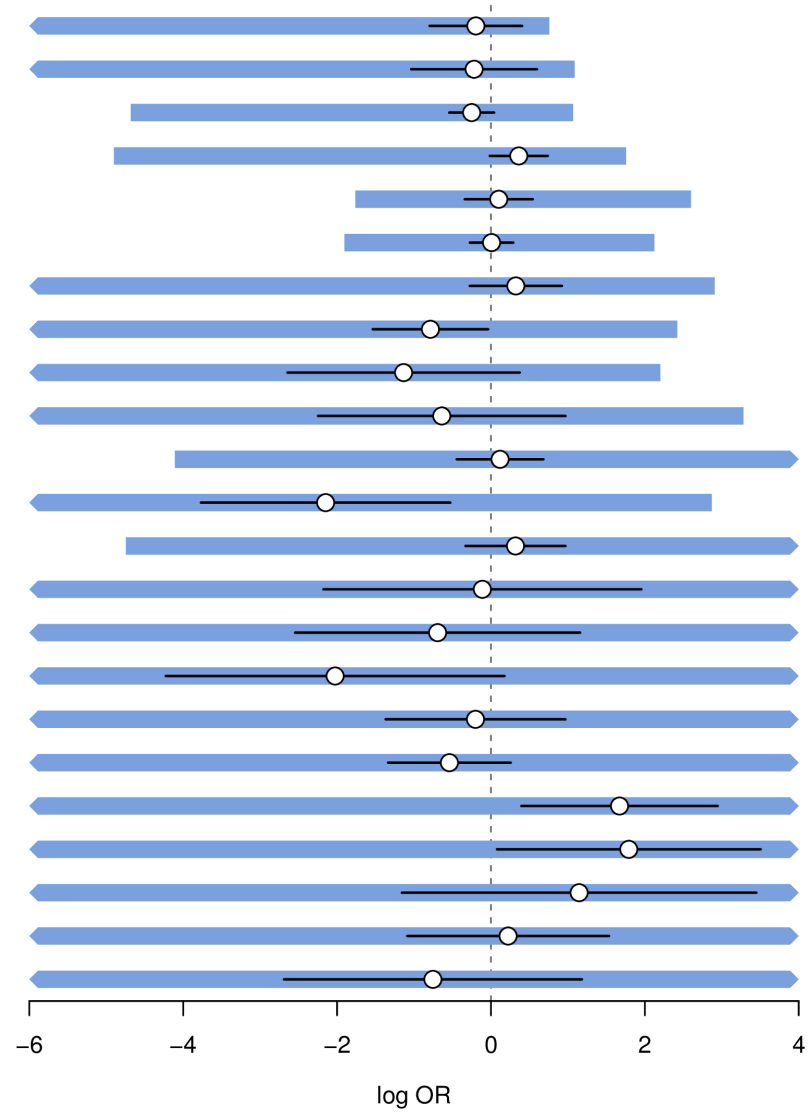
How much would the evidence have to change before we reach a new recommendation?

Positive recommendation for VTV

Threshold results for BPD and mortality

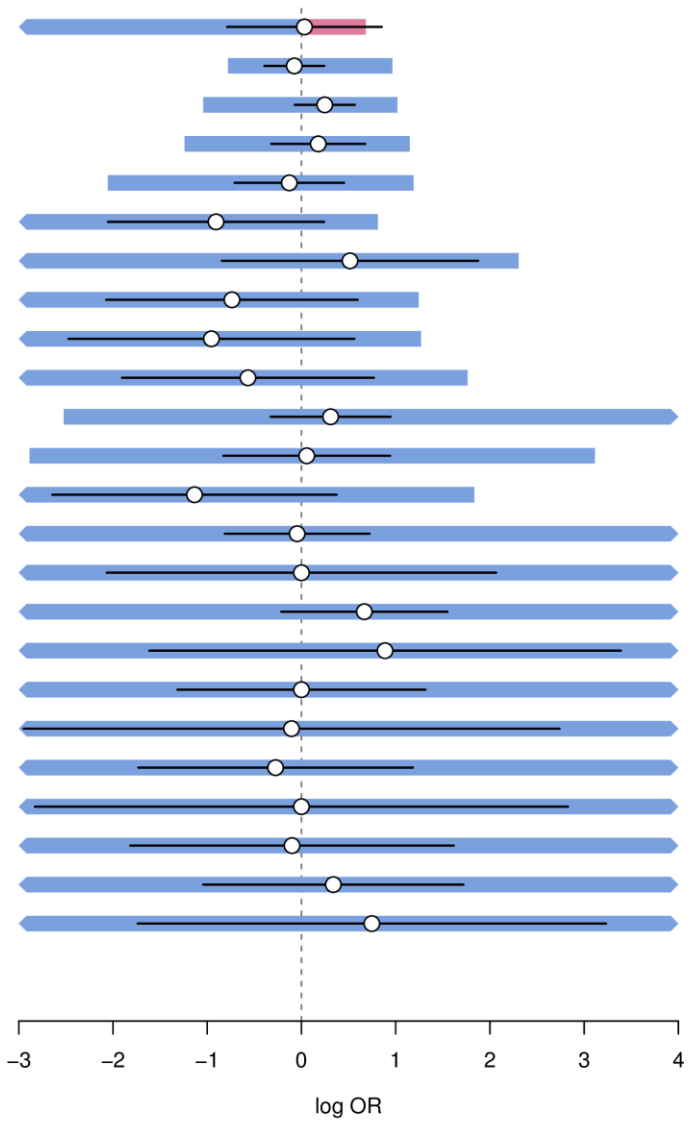
BPD – best ranked intervention (VTV, 5)

Study (contrast)	log OR	95% Confidence Interval	Invariant Interval			Sel	Perf	Det	Att	Rep	Oth
D'Angio 2005 (5 vs. 4)	−0.196	(−0.798, 0.406)	–	(NT, 0.759)	2	U	H	L	L	U	H
Singh 2006 (5 vs. 3)	−0.219	(−1.04, 0.599)	–	(NT, 1.09)	3	U	H	L	L	U	H
Baumer 2000 (3 vs. 1)	−0.250	(−0.542, 0.0420)	3	(−4.68, 1.07)	1	U	H	L	L	U	L
Courtney 2002 (4 vs. 2)	0.362	(−0.0152, 0.739)	4	(−4.90, 1.76)	2	U	H	L	U	U	H
Bereseford 2000 (3 vs. 1)	0.102	(−0.340, 0.544)	3	(−1.76, 2.60)	2	L	H	L	L	U	L
Johnson 2002 (2 vs. 1)	0.0079	(−0.274, 0.290)	2	(−1.90, 2.12)	1	U	H	L	L	L	H
Moriette 2001 (4 vs. 2)	0.324	(−0.275, 0.922)	4	(−9.18, 2.91)	2	L	H	L	L	L	H
Gerstmann 1996 (2 vs. 1)	−0.786	(−1.54, −0.0361)	2	(−8.43, 2.42)	3	H	H	L	L	U	H
Dunman 2012 (5 vs. 3)	−1.13	(−2.64, 0.374)	–	(NT, 2.20)	3	U	H	L	L	U	L
Lista 2004 (5 vs. 3)	−0.639	(−2.25, 0.969)	–	(NT, 3.28)	3	U	H	L	L	U	H
Thome 1999 (2 vs. 1)	0.119	(−0.445, 0.682)	2	(−4.11, 5.10)	1	U	H	L	L	U	L
Guven 2013 (5 vs. 4)	−2.15	(−3.77, −0.528)	–	(NT, 2.87)	2	U	H	L	L	U	H
Van reempts 2003 (2 vs. 1)	0.319	(−0.330, 0.969)	2	(−4.74, 7.32)	1	U	H	L	L	U	H
Lista 2008 (5 vs. 2)	−0.111	(−2.18, 1.96)	–	(NT, 5.54)	2	U	H	L	L	U	L
Nafday 2005 (5 vs. 4)	−0.693	(−2.55, 1.16)	–	(NT, 5.57)	2	U	H	L	L	U	L
Sinha 1997 (5 vs. 3)	−2.03	(−4.23, 0.176)	–	(NT, 4.65)	3	U	H	L	L	U	H
Craft 2003 (4 vs. 2)	−0.201	(−1.37, 0.969)	4	(−36.0, 7.03)	2	L	H	L	H	U	L
Reyes 2006 (4 vs. 4)	−0.540	(−1.34, 0.257)	–	(NT, 8.35)	3	U	H	L	L	U	L
Durand 2001 (4 vs. 2)	1.67	(0.395, 2.95)	4	(−14.4, 11.2)	2	U	H	L	L	U	H
Vento 2005 (4 vs. 2)	1.79	(0.0787, 3.50)	4	(−28.2, 17.7)	2	U	H	L	L	U	L
Salvo 2012 (4 vs. 2)	1.15	(−1.16, 3.45)	4	(−64.9, 27.4)	2	L	H	L	L	U	L
Unal 2017 (5 vs. 5)	0.223	(−1.09, 1.53)	3	(−100, NT)	–	U	H	L	L	U	L
Ozdemir 2017 (5 vs. 5)	−0.754	(−2.69, 1.18)	–	(NT, 111)	3	U	H	L	L	U	H



Mortality – best ranked intervention (VTV, 5)

Study (contrast)	log OR	95% Confidence Interval		Invariant Interval		Sel	Perf	Det	Att	Rep	Oth
D'Angio 2005 (5 vs. 4)	0.0321	(−0.788, 0.853)	–	(NT, 0.683)	4	U	H	L	L	U	H
Johnson 2002 (2 vs. 1)	−0.0758	(−0.394, 0.242)	2	(−0.780, 0.964)	1	U	H	L	L	L	H
Baumer 2000 (3 vs. 1)	0.247	(−0.0719, 0.567)	3	(−1.04, 1.02)	2	U	H	L	L	U	L
Courtney 2002 (4 vs. 2)	0.178	(−0.320, 0.677)	4	(−1.24, 1.15)	2	U	H	L	U	U	H
Moriette 2001 (4 vs. 2)	−0.129	(−0.710, 0.452)	4	(−2.06, 1.19)	2	L	H	L	L	L	H
Singh 2006 (5 vs. 3)	−0.907	(−2.05, 0.241)	–	(NT, 0.811)	2	U	H	L	L	U	H
Piotrowski 2007 (5 vs. 4)	0.515	(−0.845, 1.88)	–	(NT, 2.30)	4	U	H	L	L	U	H
Piotrowski 1997 (5 vs. 1)	−0.738	(−2.07, 0.597)	–	(NT, 1.24)	2	U	H	L	L	U	H
Guven 2013 (5 vs. 4)	−0.956	(−2.47, 0.561)	–	(NT, 1.27)	4	U	H	L	L	U	H
Lista 2004 (5 vs. 3)	−0.568	(−1.91, 0.769)	–	(NT, 1.76)	2	U	H	L	L	U	H
Van reempts 2003 (2 vs. 1)	0.309	(−0.328, 0.947)	2	(−2.52, 4.49)	1	U	H	L	L	U	H
Bernstein 1996 (4 vs. 1)	0.0561	(−0.829, 0.941)	4	(−2.89, 3.11)	1	L	H	L	L	U	L
Dunman 2012 (5 vs. 3)	−1.13	(−2.64, 0.374)	–	(NT, 1.83)	2	U	H	L	L	U	L
Thome 1999 (2 vs. 1)	−0.0455	(−0.814, 0.723)	2	(−4.17, 6.04)	1	U	H	L	L	U	L
Chowdhury 2013 (5 vs. 4)	0	(−2.07, 2.07)	–	(NT, 4.13)	4	U	H	L	L	U	H
Bereseford 2000 (3 vs. 1)	0.667	(−0.215, 1.55)	3	(−9.19, 6.56)	2	L	H	L	L	U	L
Nafday 2005 (5 vs. 4)	0.887	(−1.62, 3.39)	–	(NT, 6.94)	4	U	H	L	L	U	L
Salvo 2012 (4 vs. 2)	0	(−1.32, 1.32)	4	(−9.89, 6.77)	2	L	H	L	L	U	L
Lista 2008 (5 vs. 2)	−0.105	(−2.95, 2.74)	–	(NT, 7.65)	2	U	H	L	L	U	L
Durand 2001 (4 vs. 2)	−0.274	(−1.73, 1.18)	4	(−12.4, 8.02)	2	U	H	L	L	U	H
Sinha 1997 (5 vs. 3)	0	(−2.83, 2.83)	–	(NT, 10.4)	2	U	H	L	L	U	H
Craft 2003 (4 vs. 2)	−0.100	(−1.82, 1.62)	4	(−16.9, 11.4)	2	L	H	L	H	U	L
Rettwitz−volk 1998 (2 vs. 1)	0.338	(−1.04, 1.72)	2	(−13.0, 20.0)	1	U	H	L	L	U	H
Vento 2005 (4 vs. 2)	0.747	(−1.74, 3.23)	4	(−34.5, 24.9)	2	U	H	L	L	U	L
Gerstmann 1996 (2 vs. 1)	−Inf	(–, –)	–	(NT, NT)	–	H	H	L	L	U	H
Ogawa 1993 (2 vs. 1)	−Inf	(–, –)	–	(NT, NT)	–	U	H	L	L	U	H



○ log OR — 95% Confidence Interval ▬ Invariant Interval

Positive recommendation for VTV

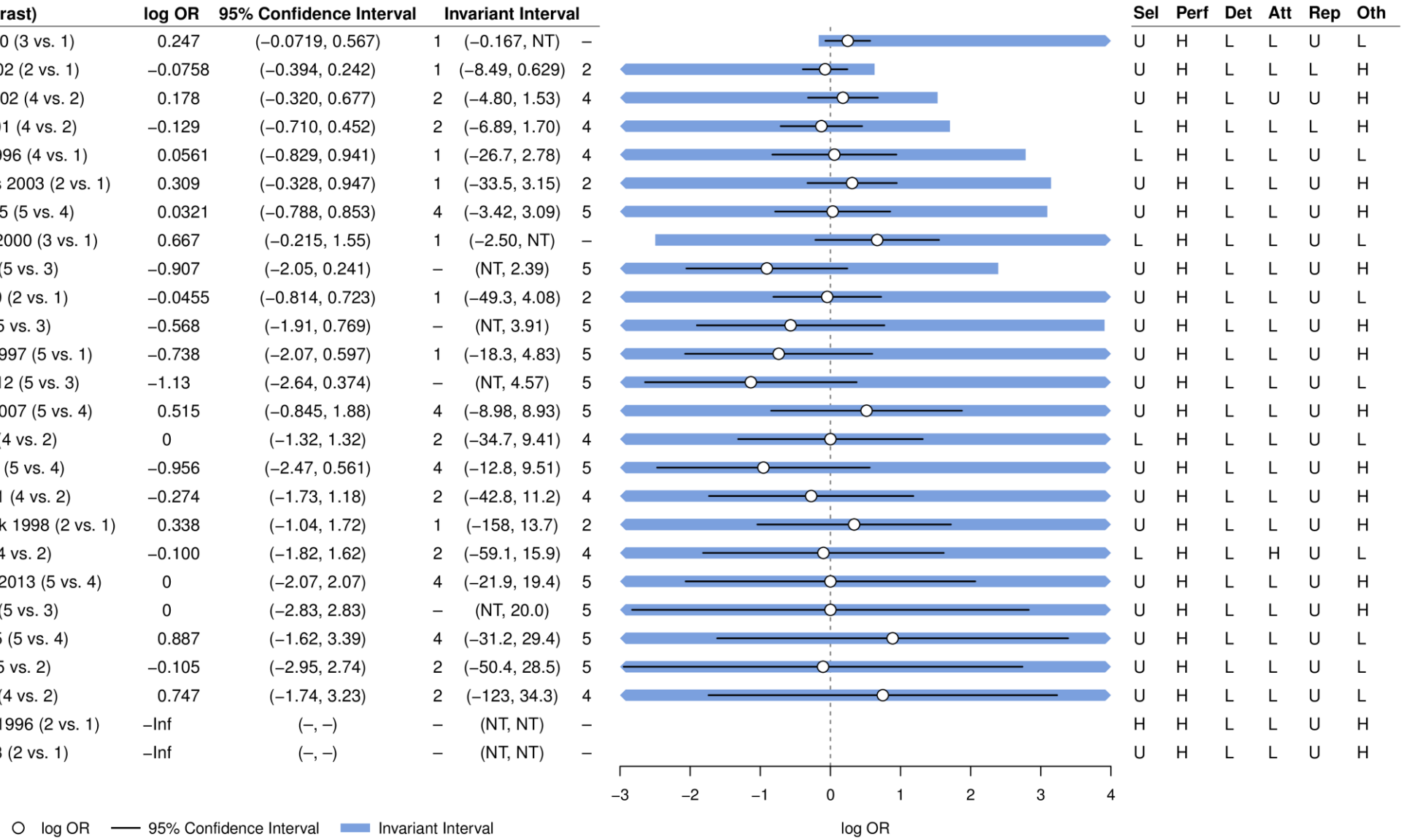
- Robust on BPD outcome, despite high risk of bias
- Sensitive to the level of uncertainty in a single study (D'Angio 2005) for mortality outcome
  - Could lead to SIMV being ranked best for mortality
  - No "significant" difference between top two treatments for mortality
    - log odds ratio for VTV vs. SIMV is –0.21 (95% CrI: –0.67, 0.25)

Do-not-do recommendation for SPLV

Threshold results for mortality

Mortality – worst ranked intervention (SPLV, 3)

Study (contrast)	log OR	95% Confidence Interval		Invariant Interval		Sel	Perf	Det	Att	Rep	Oth
Baumer 2000 (3 vs. 1)	0.247	(–0.0719, 0.567)	1	(–0.167, NT)	–	U	H	L	L	U	L
Johnson 2002 (2 vs. 1)	–0.0758	(–0.394, 0.242)	1	(–8.49, 0.629)	2	U	H	L	L	L	H
Courtney 2002 (4 vs. 2)	0.178	(–0.320, 0.677)	2	(–4.80, 1.53)	4	U	H	L	U	U	H
Moriette 2001 (4 vs. 2)	–0.129	(–0.710, 0.452)	2	(–6.89, 1.70)	4	L	H	L	L	L	H
Bernstein 1996 (4 vs. 1)	0.0561	(–0.829, 0.941)	1	(–26.7, 2.78)	4	L	H	L	L	U	L
Van reempts 2003 (2 vs. 1)	0.309	(–0.328, 0.947)	1	(–33.5, 3.15)	2	U	H	L	L	U	H
D'Angio 2005 (5 vs. 4)	0.0321	(–0.788, 0.853)	4	(–3.42, 3.09)	5	U	H	L	L	U	H
Bereseford 2000 (3 vs. 1)	0.667	(–0.215, 1.55)	1	(–2.50, NT)	–	L	H	L	L	U	L
Singh 2006 (5 vs. 3)	–0.907	(–2.05, 0.241)	–	(NT, 2.39)	5	U	H	L	L	U	H
Thome 1999 (2 vs. 1)	–0.0455	(–0.814, 0.723)	1	(–49.3, 4.08)	2	U	H	L	L	U	L
Lista 2004 (5 vs. 3)	–0.568	(–1.91, 0.769)	–	(NT, 3.91)	5	U	H	L	L	U	H
Piotrowski 1997 (5 vs. 1)	–0.738	(–2.07, 0.597)	1	(–18.3, 4.83)	5	U	H	L	L	U	H
Dunman 2012 (5 vs. 3)	–1.13	(–2.64, 0.374)	–	(NT, 4.57)	5	U	H	L	L	U	L
Piotrowski 2007 (5 vs. 4)	0.515	(–0.845, 1.88)	4	(–8.98, 8.93)	5	U	H	L	L	U	H
Salvo 2012 (4 vs. 2)	0	(–1.32, 1.32)	2	(–34.7, 9.41)	4	L	H	L	L	U	L
Guven 2013 (5 vs. 4)	–0.956	(–2.47, 0.561)	4	(–12.8, 9.51)	5	U	H	L	L	U	H
Durand 2001 (4 vs. 2)	–0.274	(–1.73, 1.18)	2	(–42.8, 11.2)	4	U	H	L	L	U	H
Rettwitz–volk 1998 (2 vs. 1)	0.338	(–1.04, 1.72)	1	(–158, 13.7)	2	U	H	L	L	U	H
Craft 2003 (4 vs. 2)	–0.100	(–1.82, 1.62)	2	(–59.1, 15.9)	4	L	H	L	H	U	L
Chowdhury 2013 (5 vs. 4)	0	(–2.07, 2.07)	4	(–21.9, 19.4)	5	U	H	L	L	U	H
Sinha 1997 (5 vs. 3)	0	(–2.83, 2.83)	–	(NT, 20.0)	5	U	H	L	L	U	H
Nafday 2005 (5 vs. 4)	0.887	(–1.62, 3.39)	4	(–31.2, 29.4)	5	U	H	L	L	U	L
Lista 2008 (5 vs. 2)	–0.105	(–2.95, 2.74)	2	(–50.4, 28.5)	5	U	H	L	L	U	L
Vento 2005 (4 vs. 2)	0.747	(–1.74, 3.23)	2	(–123, 34.3)	4	U	H	L	L	U	L
Gerstmann 1996 (2 vs. 1)	–Inf	(–, –)	–	(NT, NT)	–	H	H	L	L	U	H
Ogawa 1993 (2 vs. 1)	–Inf	(–, –)	–	(NT, NT)	–	U	H	L	L	U	H



Do-not-do recommendation for SPLV

- Worst-place ranking of SPLV for mortality was robust, despite high risk of bias

Impact on decision-making

Positive recommendation (VTV)

- First-place ranking for BPD was robust
  - Placated concerns over potential biases in the evidence
- First-place ranking for mortality was sensitive to imprecision from a single study
  - Committee considered this when formulating the positive recommendation

Do-not-do recommendation (SPLV)

- Last-place ranking for mortality was robust
  - Provided reassurance to the committee for this do-not-do recommendation

Conclusions

- Evidence quality and risk of bias are not sufficient to assess robustness of decisions
- Threshold analysis provides insight into the effects of changes in the evidence on treatment decisions
  - We can have more confidence in recommendations where thresholds are large
  - We can focus attention on the quality of decision-sensitive evidence
- More complex analyses can investigate specific concerns in the evidence
- Can be used with a range of decision rules or for decisions based on cost-effectiveness

Thank You

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Phillippo DM et al. (2018). *Sensitivity of treatment recommendations to bias in network meta-analysis*. J Royal Stat Soc A, 181:843-867. doi:10.1111/rssa.12341

Phillippo DM et al. (2019). *Confidence in recommendations based on Network Meta-Analysis: threshold analysis as an alternative to GRADE NMA in guideline development.* Ann Intern Med, 170(8):538-546. doi:10.7326/M18-3542

R package *nmathresh* package available on CRAN.

Final guideline available from **nice.org.uk/guidance/ng124**.